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Original Article

Prognostic value of progesterone receptor status in Chinese breast cancer patients treated with tamoxifen

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Abstract: The absence of progesterone receptor (PR) is attributable to low serum estrogen, low level of functional estrogen receptor (ER) nuclear and high expression of growth factors. Understanding the value of PR in human epidermal growth factor 2 (HER2) negative and ER positive breast cancer treat with tamoxifen (TAM) is important as TAM treatment is the main approach for ER+/HER2-breast cancer therapy. The aim of this study is to compare the efficacy of TAM treatment for PR+ and PR- breast cancer among ER+/HER2- cases. Clinical and follow-up data (the median follow-up time was 41 months) of 250 being ER+/HER2- breast cancer patients treated at Sichuan cancer hospital from 2005 to 2009 were collected, then the differences of overall survival (OS) and disease free survival (DFS) for PR+ and PR- cases with or without TAM therapy were analyzed by Kaplan-Meier and COX proportional hazards model. The results showed that the OS and DFS were similar between PR+ and PR- patients who without TAM treatment (P>0.05). Among patients who received TAM treatment, the 5-year OS were 91.2% and 68.2% in PR+ and PR- cases respectively (P=0.018) and the 5-year DFS were 81.2% and 63.1% respectively (P=0.030). PR- cases had higher risk for death, recurrence and metastasis (adjusted HR_{OS}=3.558, 95% *CI*: 1.061-11.932; adjusted HR_{DFS}=2.498, 95% *CI*: 1.002-6.229) compared with PR+ cases. PR expression status significantly affected the efficacy of TAM endocrine treatment in ER+/HER2- breast cancer patients. PR-patients could get less benefit from the TAM treatment than PR+ patients.

Keywords: Breast neoplasms, receptors, progesterone, tamoxifen, prognosis

Introduction

The expression of estrogen receptor (ER) is an important indicator of guiding endocrine therapy (ET) strategies in breast cancer patient, and it is a valuable prognostic factor of ET. Progesterone receptor (PR) is regulated by estrogen, and the expressions of ER and PR are closely positively correlated [1]. It has been showed that the proportion of ER and PR double positive (ER+/PR+) or negative (ER-/PR-) patients was as high as 72% [2]. There was 25% tumor being ER-positive, PR-negative (ER+/PR-) and the formation mechanism is currently controversial. There were three main hypotheses: (i) the functional defect or the low positive expression of endogenous ER made PR synthesis failed [3]; (ii) the low expression level of endogenous estrogen caused the deficiency of ER-complex synthesis, which was the precursor of PR synthesis [4, 5]; (iii) the excessive expression of human epidermal growth factor 2 (HER2) could decrease the expression of PR in ER positive breast cancer cell lines [6-8].

Tamoxifen (TAM) is the most commonly used drug in breast cancer ET. It competed with estradiol in breast tissues to bind to the hormone receptor (HR), reducing the stimulation of estrogen to breast cells. Although aromatase inhibitors (AIs) had been recommended for adjuvant ET for postmenopausal patients in China since 2003, TAM still was the most common ET medicine as AIs were extremely expensive and were not listed on the medical insurance formulary. As reported from Australian [9, 10], the nation-wide multicenter 10-year retrospective clinical study in China showed that 80.3% (1283/1598) of the patients were given anti-estrogens (TAM and toremifen) as the primary ET agents during 1999 and 2008 [11].

Several studies from western countries demonstrated that TAM was less efficacious for ER+/PR- tumors than ER+/PR+ tumors, which were characterized by aggressive behavior and TAM resistance [12-14]. However, The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) study showed the benefit of adjuvant TAM in reducing the risk of recurrence regardless of PR status in ER-positive breast cancer [15]. Thus, the conclusion is still inconsistent according to previous studies. Additionally, endocrine therapy is recommended for ER positive tumor regardless of PR status in China, so it is valuable to access the prognostic value of PR status among ER positive breast cancer patients treated with TAM. To our knowledge, only two previous studies had assessed the relationship between PR statues and ET outcome in ER positive breast cancer in China [16, 17]. In addition, it has been revealed that HER2 positive expression could enhance the biological and pathological malignancy of breast tumors and significantly increase the tumor resistance to TAM [2, 3]. Thus, it's necessary to evaluate the treated effect of TAM on PR negative tumor stratified on HER2 expression. However, the limited studies from China had not considered the expression of HER2. Therefore, in this study, we selected ER-positive and HER2-negative breast cancer patients to observe their TAM treatment outcome with different PR expression, and then evaluate the prognostic value of PR status for TAM treatment.

Materials and methods

Subjects

The study protocol was approved by the Institutional Review Board of Sichuan University. The clinical data of female patients who had been pathologically diagnosed with primary breast cancer and treated with breast surgery at Sichuan cancer hospital from year 2005 to 2010 was retrospectively collected. ER, PR, and HER2 status of the patients were abstracted from medical records, which were determined by immunohistochemical (IHC) assay at the pathology department of Sichuan cancer hospital. Positivity of ER and PR status was defined as ≥1% of tumor cells presenting positive nuclear staining. The results of HER2 were scored semi-quantitatively according to the estimated percent of positively stained tumor cell nuclei and the intensity of nuclear staining (- for no staining, +1 for weak intensity, +2 for intermediate intensity, and +3 for strong intensity). Results of "-" or "+1" were determined as HER2 negative and "3+" as positive. If the IHC results were "2+", the fluorescence in situ hybridization (FISH) was applied. Finally, 250 patients with ER+/HER2- tumor were included in our study.

Information collection

The following data of clinical information were collected by designed case report forms from medical record: (1) general information: including date of diagnosis, date of hospital admission; (2) demographic characteristics: including age, menopausal status; (3) anthropometric index: height, weight; (4) pathological features: pathological type, tumor size, axillary lymph node metastasis, and TNM stage; (5) treatment information: treatment protocol of surgery, radiotherapy, chemotherapy and ET. Specifically, the TNM stage was categorized using the 2003 American Joint Committee on Cancer (AJCC) TNM System. Body mass index (BMI) was calculated as body weight (kg)/height (m^2) and used as a measure of general obesity. The menopausal status was determined as the patients were diagnosed as breast cancer without any treatment, such as chemotherapy. A woman was defined as postmenopausal if she had undergone natural menopause (continuously experienced 12 month without a menstrual cycle before any endocrine treatment or ovariectomy), bilateral oophorectomy, or irradiation of the ovaries before 50 years. Additionally, if a woman was aged 50 or older and no longer experienced menstruation, she would be considered postmenopausal.

Follow-up

Clinical follow-ups were performed to monitor the outcome of the patients, including recurrence, metastasis, and death. The study ended on March 30th, 2013, and the median follow-up time of the 250 patients was 41 months (range: 12 to 93 months). Overall survival (OS) was defined as the period from the first day of surgical treatment to the date of death. Disease free survival (DFS) was defined as the period from the first day of surgical treatment to the date when cancer cell recurrence or metastasis was observed.

Table 1. Clinical information of patients

	Without TAM treatment (N=76)			With TAM treatment (N=174)			P^b
	PR+ (N=55)	PR- (N=21)	P^a	PR+ (N=138)	PR- (N=36)	P^a	
Age (years)							
Mean ± SD	46.62±11.00	50.71±8.92	0.132	47.02±11.19	49.72±9.63	0.187	0.153
Menopausal status							
Premenopausal	37 (67.3%)	8 (38.1%)	0.020	97 (70.3%)	17 (47.2%)	0.009	0.340
Postmenopausal	18 (32.7%)	13 (61.9%)		41 (29.7%)	19 (52.8%)		
BMI (kg/m^2)							
<24	33 (60.0%)	11 (52.4%)	0.609	87 (63.0%)	22 (61.1%)	0.848	0.478
≥24	22 (40.0%)	10 (47.6%)		51 (37.0%)	14 (38.9%)		
Pathological type							
Invasive ductal carcinoma	51 (92.7%)	18 (85.7%)	0.387	121 (87.7%)	30 (83.3%)	0.580	0.370
Others	4 (7.3%)	3 (14.3%)		17 (12.3%)	6 (16.7%)		
Tumor size (mm)							
<20	27 (49.1%)	9 (42.9%)	0.629	60 (43.5%)	14 (38.9%)	0.150	0.346
20~50	20 (36.4%)	7 (33.3%)		64 (46.4%)	14 (38.9%)		
>50	8 (14.5%)	5 (23.8%)		14 (10.1%)	8 (22.2%)		
Lymph node metastasis							
0	21 (38.2%)	7 (33.3%)	0.902	64 (46.4%)	17 (47.2%)	0.382	0.057
1~3	21 (38.2%)	10 (47.6%)		32 (23.2%)	12 (33.3%)		
4~9	10 (18.2%)	3 (14.3%)		26 (18.8%)	3 (8.3%)		
≥10	3 (5.5%)	1 (4.8%)		16 (11.6%)	4 (11.1%)		
TNM stage							
TNM I & II	47 (85.5%)	18 (85.7%)	1.000	124 (89.9%)	29 (80.6%)	0.151	0.601
TNM III & IV	8 (14.5%)	3 (14.3%)		14 (10.1%)	7 (19.4%)		
Operation therapy							
Radical mastectomy	37 (67.3%)	11 (52.4%)	0.290	86 (62.3%)	25 (69.4%)	0.428	0.924
Breast conservative surgery	18 (32.7%)	10 (47.6%)		52 (37.7%)	11 (30.6%)		
Radiotherapy							
Yes	24 (43.6%)	12 (57.1%)	0.316	71 (51.4%)	15 (41.7%)	0.351	0.765
No	31 (56.4%)	9 (42.9%)		67 (48.6%)	21 (53.8%)		
Chemotherapy							
Yes	50 (90.9%)	21 (100.0%)	0.314	132 (95.7%)	36 (100.0%)	0.347	0.267
No	5 (9.1%)	0		6 (4.3%)	0		

[a]*P*-value for PR+ and PR- patients, [b]*P*-value for patients without TAM treatment and patients with TAM treatment.

Statistical analysis

The *t*-test and the chi-square test were used to compare the age, menopausal status, BMI, pathology, tumor size, axillary lymph node metastasis, TNM stage and treatment information of PR+ and PR- patients who received or did not receive TAM treatment. The Log-rank test was applied to compare the 5-year survival rate between PR+ and PR- patients. The Kaplan-Meier method was applied to make survival curves. COX proportional hazard model was performed to compare the DFS and OS between PR+ and PR- patients by adjusting confounding factors. Data were analyzed with Stata 12.0 software. All *p*-values were subjected to a two-tailed test with an alpha level of 0.05 for significance testing.

Results

Clinical characteristics of breast cancer patients

The mean age of the patients was 47.63±10.79 years old (range: 23-81). A total of 159 (63.6%)

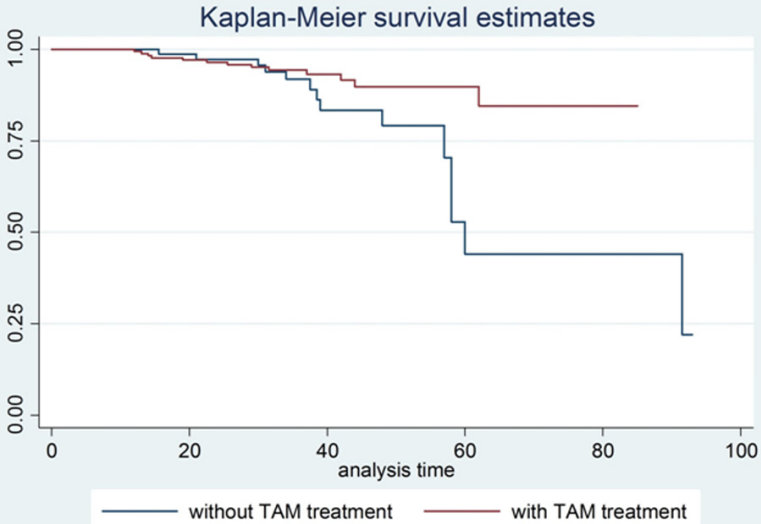

Figure 1. Overall survival of patients who with TAM treatment and who without TAM treatment.

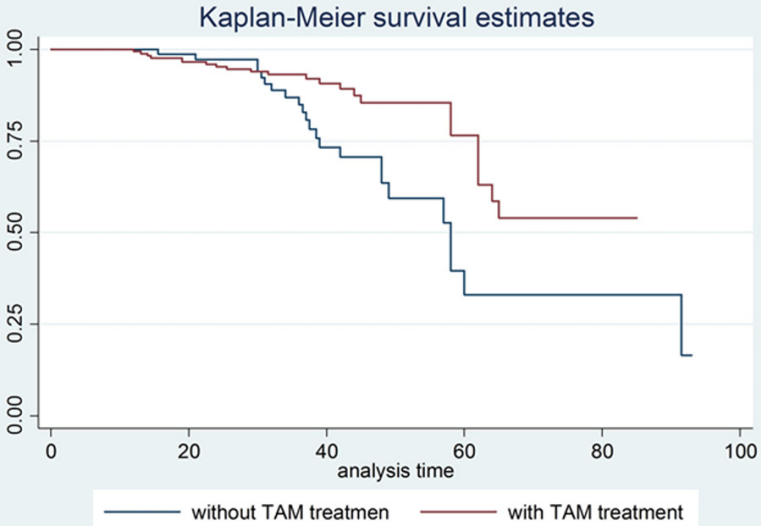

Figure 2. Disease free survival of patients who with TAM treatment and who without TAM treatment.

patients were premenopausal, and 91 (36.4%) were postmenopausal. Among the 250 ER+/HER2-patients, 220 (88.0%) cases were invasive ductal carcinoma. The distribution of TNM stage was 14 at stage I (5.6%), 204 at stage II (81.6%), 30 at stage III (12.0%), and 2 at stage IV (0.8%) respectively.

Comparison of patients who with tamoxifen treatment and who without tamoxifen treatment

A total of 174 patients (69.6%) did receive TAM treatment until the latest follow-up, while 76 (30.4%) did not receive any TAM treatment. There were no significant differences between these two group patients in age, menopausal status, BMI, pathological features (pathological type, tumor size, axillary lymph node metastasis, and TNM stage), or other treatment information (surgery, radiotherapy, and chemotherapy) (P>0.05) (**Table 1**).

The OS and DFS curves of patients who with TAM treatment and who without TAM treatment were shown in **Figures 1** and **2** respectively. The 5-year OS of patients with TAM treatment (87.1%) was significantly higher than those without TAM treatment (61.3%) (P=0.004). The similar results were also observed for the 5-year DFS (with vs. without TAM treatment: 74.2% vs. 53.2%) (P=0.007). Multivariate analysis indicated that TAM treatment significantly decreased the risk of death, recurrence, and metastasis (the adjusted HR_{OS}=0.327, 95% *CI*: 0.144-0.745; the adjusted HR_{DFS}= 0.314, 95% *CI*: 0.164-0.601) (**Table 2**).

Comparison of survival outcome between PR+ and PR- patients

There were 55 PR+ cases (72.4%) and 21 PR- (27.6%) cases who did not receive TAM treatment, while 138 PR+ (79.3%) and 36 PR- cases (20.7%) who received TAM treatment. Apart from menopausal status, the distribution of other clinical risk factors was not significantly different between PR+ and PR- patients (P>0.05) (**Table 1**).

There was no significant difference in OS or DFS between PR+ and PR- patients who did not receive TAM treatment (P>0.05). For patients who received TAM treatment, the 5-year OS of PR+ (91.2%) was remarkably higher than that of PR- cases (68.2%) (P=0.018). The 5-year DFS for PR+ patients (81.2%) was also higher

Table 2. Survival outcome of patients without and with TAM treatment

		N	Overall survival			Disease free survival		
			5-year OS	HR_{crude} (95% *CI*)*	$HR_{adjusted}$ (95% *CI*)**	5-year DFS	HR_{crude} (95% *CI*)	$HR_{adjusted}$ (95% *CI*)**
Non-TAM treatment	Overall	76	61.3%	1.000	1.000	53.2%	1.000	1.000
TAM treatment	Overall	174	87.1%	0.437 (0.202-0.943)	0.327 (0.144-0.745)	74.2%	0.456 (0.254-0.820)	0.314 (0.164-0.601)
	Log-rank		8.140			7.368		
	P		0.004			0.007		
Non-TAM treatment	PR+	55	66.3%	1.000	1.000	54.5%	1.000	1.000
	PR-	21	59.1%	2.399 (0.505~11.407)	0.963 (0.107~8.699)	51.6%	2.315 (0.596~7.648)	0.577 (0.097~3.444)
	Log-rank		1.161			1.004		
	P		0.281			0.316		
TAM treatment	PR+	138	91.2%	1.000		81.2%	1.000	1.000
	PR-	36	68.2%	3.396 (1.136~10.151)	3.558 (1.061~11.932)	63.1%	2.378 (1.024~5.523)	2.498 (1.002~6.229)
	Log-rank		5.551			4.718		
	P		0.018			0.030		

*Hazards ratio (HR) and 95% confidence intervals (*CI*) obtained from a univariate COX proportional hazards regression model; **HR and 95% *CI* obtained from a multivariate COX proportional hazards regression model adjusted for age, BMI, pathological type, TNM stage, operation therapy, radiotherapy and chemotherapy.

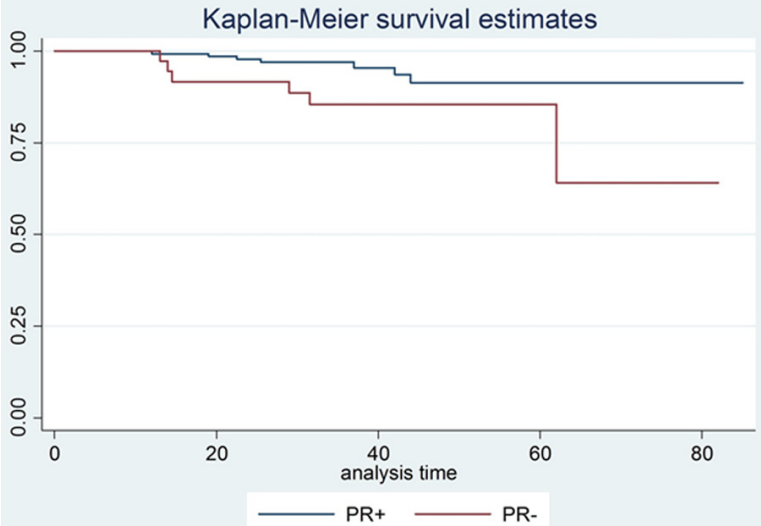

Figure 3. Overall survival of PR+ and PR- patients who with TAM treatment.

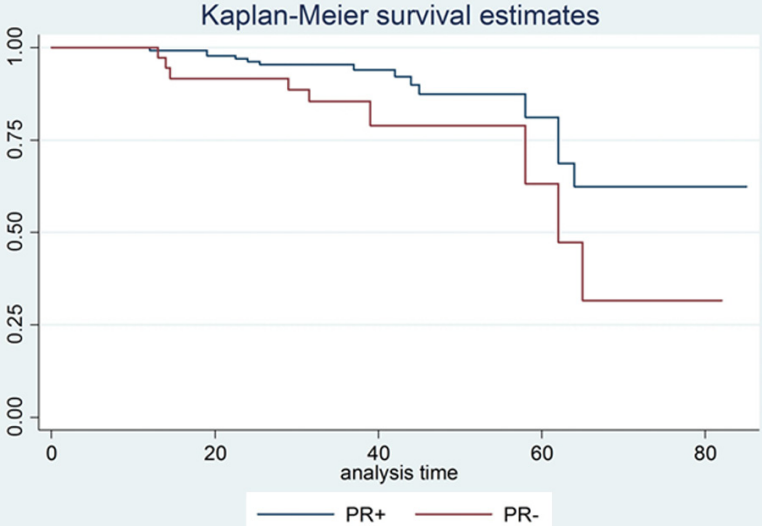

Figure 4. Disease free survival of PR+ and PR- patients who with TAM treatment.

than PR- patients (63.1%) (*P*=0.030). The OS and DFS curves of PR+ and PR- patients who received TAM treatment were shown in **Figures 3** and **4** respectively. The multivariate COX regression model showed that the risk of death, recurrence and metastasis was all higher in the PR- patients than in the PR+ patients (the adjusted HR_{OS}=3.558, 95% *CI*: 1.061-11.932; the adjusted HR_{DFS}=2.498, 95% *CI*: 1.002-6.229) (**Table 2**).

Discussion

This study revealed that ER+/HER2- breast cancer patients who received TAM treatment had lower risk of death and relapse. Furthermore, PR expression status was associated with the efficacy of TAM treatment that the therapeutic effect was worse in PR- patients than in PR+ patients. PR+ patients had better OS and DFS than PR- patients who received TAM treatment. Our findings were in agreement with previous studies that showed PR loss identified ER+ breast cancer at high risk of relapse or death [12, 13]. Our results indicated that PR expression status could be used as an important index to predict the efficacy of TAM treatment for ER+/HER2- breast cancer patients.

Few studies have examined potential prognostic value of progesterone receptor in breast cancer patients treated with TAM. Cancello [13]'s study including 4,837 patients with Luminal B breast tumor revealed that, regardless of HER2 expression, negative PR expression is an independent adverse factor of TAM resistance influencing death or recurrence of Luminal B breast cancer (HROS=1.47, 95% CI: 1.10-1.96; HRDFS=1.71, 95% CI: 1.25-2.35). Recently, the British Columbia Cancer Agency (BCCA) TAM-treated cohort (BCCA-TAM) [14] and the Grupo Español de Investigación en Cáncer de Mama (GEICAM) 9906 trial [14] data reported that semi-quantitative IHC expression of PR added important prognostic value in Luminal A breast cancer. In the both data, Luminal A tumors with low PR-positive tumor cells (<20%) showed significantly poorer survival than tumors with more than 20% of PR-positive cells. On the contrary, the meta-analysis of randomized trials from the EBCTCG that evaluated adjuvant TAM versus without TAM suggested that recurrence and death rate ratio was independent of PR status or level in ER+ tumors [15]. Similar data have also been observed in

another randomized adjuvant study [18]. In the present study, the treatment efficacy of TAM varies significantly in patients with different status of PR expression. PR- patients could get little benefit from the TAM treatment than PR+ patients.

Response to TAM therapy was related to the functional status of hormone receptors and not just their expression. Evidence from pervious study identified that ER was nonfunctional in some of ER+/PR- tumors and was unable to stimulate PR production [2, 3]. There were also several lines of evidence suggesting growth factor signaling pathways could also cause PR down regulation [1, 2]. While in this study, all tumors were HER2 negative, so there might be little or no effect of growth factors. ER existed in two isoforms in breast cancer tumors: ER-α and ER-β. The current method used to determine breast cancer treatment was based on the evaluation of ER-α status by IHC, but studies had identified that ER-β status could provide additional information that the score of ER-β protein was correlated with the score of PR protein [19, 20]. The correlation between ER-β protein and PR protein expression represented their possible association in mechanism. The ER-β protein expression might reflect the function of ER nucleus and PR synthesis pathway. So for ER+/PR- breast cancer cases, the level of ER-β protein might have prognostic implication in survival and the effect of TAM therapy. However, our study had not detected the ER-β protein levels as the limitation of study design. Research on the mechanism of ER-β and PR, the association of ER-β and PR and the effect of TAM therapy is needed in the future study.

A large randomized trial (BIG 1-98 trial) had compared the treatment efficacy between letrozole and TAM as adjuvant treatment of patients with hormone receptor positive breast cancer. The results revealed patients treated with letrozole had a better outcome than those treated with TAM regardless of their PR status [21]. Thus, AIs might be good choice for ER+/PR- tumors compared with TAM. However, AIs should not be used in premenopausal patients because the estrogen withdrawal would cause negative feedback on the pituitary, which resulted in surges of estrogen and increased breast cancer growth. For these ER+/PR- premenopausal breast cancer cases, estrogen withdrawal can be achieved by ovariectomy or ovarian castration therapy and then followed by AIs.

There was no significant difference in prognosis between PR+ and PR- patients who did not receive the TAM treatment. This may be influenced by the presence of similar demographic and pathological features of PR+ and PR- patients. It has been reported that ER+/PR- patients had more malignant characteristics, like later clinical stage and higher HER2 positive expression compared with ER+/PR+ breast cancer patients. However, our results did not find those differences. Zhou [22] and Huang [1] reported that the differences of pathological and biological features among PR- and PR+ tumors were related to the level of ER positivity and HER2 positivity. PR negative tumors showed more malignant characteristics if the ER expression was less positive and HER2 expression was high positive. Therefore, the conflict between our results and published studies may due to all the tumors in our study were HER2 negative. Our study also found that there were more postmenopausal women in the ER+/PR- tumors than the ER+/PR+ tumors, which was consistent with previous studies [4, 5].

There were several potential limitations in this study. First, it was a retrospective study and the TAM treatment was not determined on a randomized basis. Second, although the study focused on HER2 receptors which contributing to TAM resistance, additional epidermal growth factor receptors (EGFR), like epidermal growth factor receptor 1 (HER1) might also contribute, and such factors were not analyzed.

In conclusion, our study found that lack of PR expression could affect the efficacy of TAM endocrine treatment in ER+ breast cancer patients even though considered the contribution of growth factor receptors. Targeted therapies for ER+/PR- subtype seem promising and warrant further exploration.

Disclosure of conflict of interest

None.

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